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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GREENE, JAIME M	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,481	KURODA ET AL.	
	Examiner	Art Unit	
	Jaime M. Greene	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *2-7, 10-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 6-8* is/are rejected.

7)☐ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed 9/26/07. Claims 1-11 are pending in the application. Claims 1 and 6-9 are under examination on the merits.

Withdrawn objections

2. In light of the amendment to the claims, the objection to claims 6-8 has been withdrawn.

Maintained Claim Objections

3. Claim 9 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only--, and/or, --cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits.

Response to arguments

Applicants argue that the amendment to claim 9 obviates the objection. However, the claim is drawn to a method comprising 2 or more of the methods of claims 6, 7 or 8. By requiring a combination of the methods from the claims, claim 9 is not recited in the alternative only.

Specification

4. The disclosure is objected to because of the following informalities: the specification refers to figures 1A and 1B on, for example, pg 28, line 15. However, Figure 1 is not labeled with sections A and B. Appropriate correction is required.

Affidavit or Declaration under 37 CFR 1.132

5. The Declaration under 37 CFR 1.132 filed 9/26/07 is sufficient to overcome the 102(a) and 103 rejection of claims 1 and 6-8 based upon the statement that the NPL document is by the inventors and therefore not "by another" as required by 35 USC 102(a).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1 and 6-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. The term "significantly higher" in claims 1 and 6-8 is a relative term which renders the claim indefinite. The term "significantly higher" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 112 Enablement

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1 and 6-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Teletronics Inc*, 8 USPQ2d 1217 (Fed Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986)) and *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988)).

The breadth of the claims and nature of the invention

Claims 1 and 6-8 are broadly drawn to methods of diagnosing any endometriosis-related disease by determining the expression level of histamine releasing factor (HRF) polynucleotide in an endometriotic tissue or menstrual blood biological sample and comparing the expression level with that in any normal biological sample, wherein a subject exhibiting a significantly higher HRF polynucleotide expression level when compared with any normal biological sample is indicative of a subject having any endometriosis-related disease or as a subject at risk thereof.

The nature of the invention not only involves determining the expression level of HRF in a sample from any subject, but also using that expression level to determine if a subject has any endometriosis-related disease or is at risk thereof Since the specification does not provide a definition for the term "subject", the invention broadly encompasses examining any organism. Also, since the specification does not define "endometriosis-related disease", the invention broadly encompasses diseases such as cancer and infertility.

Guidance in the Specification and Working Examples

The specification teaches collecting tissue samples from 18 patients. The specification teaches that the samples were endometriosis implants, eutopic endometrium from endometrial patients and normal endometrial tissues from patients having no endometriosis (pg 24, lines 25-30). The specification and figure 1 teach that only 3 out of 5 endometriosis patients exhibited higher HRF expression levels in the implant tissue as compared to the normal tissue (pg 28, lines 3-6). Also, figure 2 demonstrates the results from northern blot analysis of HRF expression (pg 28, lines 21-26). Figures 2A and 2B teach that the expression levels for the eutopic endometrial samples and the normal samples had approximately the same expression levels, and that only some of the endometrial implants exhibited higher expression levels as compared with the normals. Since there is no significant demonstrated increase in HRF expression levels between endometrial tissue (both eutopic and implant) samples and normal tissue samples, the data indicates that is it unpredictable to use HRF expression

levels from endometrial tissue as a means of determining the presence of endometriosis.

The specification does not teach examining HRF expression levels in patients with other endometriosis-related disorders. The specification does not teach examining HRF expression levels in other organisms. The specification does not teach what constitutes a normal expression level.

The unpredictability of the art, the state of the prior art, level of skill in the art

While the state of the art and level of skill in the art with regard to correlating gene expression with disease state is high, the level of unpredictability in associating any gene expression levels with a particular disease state is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

Oikawa (previously cited: Oikawa, et al. Journal of pathology, 2003; 199:318-323) teaches studying HRF expression in endometriotic implants and states that high HRF expression was observed in endometriotic implants when compared with normal endometriotic tissue and from eutopic endometriotic tissue from patients with endometriosis (pg 320, col 1, para 4). This indicates that HRF expression cannot be used to determine whether or not a subject has endometriosis since HRF level was considered high when compared with the eutopic endometriotic tissue from patients with endometriosis. In addition, Figure 2 demonstrates that only some of the endometriotic implant tissue samples had expression levels that were higher than normal (pg 321, col 1, Figure 2 and caption), indicating that simply determining the expression level of HRF

in any endometriotic implant tissue samples cannot be used predictably to determine if a patient has endometriosis.

Regarding comparing expression level to controls, Cheung (Cheung et al. Nature Genetics March 2003; 33:422-425) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). Therefore, since gene expression levels can vary between individuals, it is unpredictable to use any sample as a control to perform gene expression comparisons for diagnostic purposes.

The art teaches genetic expression associations are often irreproducible. Shalon (Shalon et al. US 2001/0051344 A1 Dec 13, 2001) teaches that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (see page 10, paragraph 0155). Shalon further teaches that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (see page 10, paragraph

0156). Shalon teaches that the test average pattern is compared with a control average pattern on a microarray to identify test genes which show significantly, typically at least 2 fold and up to 100 fold or more, increase or decrease in gene expression level with respect to control levels for the same gene (see page 10, paragraph 0158). Therefore the art teaches that genetic differences in individuals affect the expression levels of genes and make it difficult to provide a clear association between expression and disease.

Quantity of Experimentation

Claims 1 and 6-8 are broadly drawn to methods of diagnosing any endometriosis-related disease by determining the expression level of histamine releasing factor (HRF) polynucleotide in an endometriotic tissue or menstrual blood biological sample and comparing the expression level with that in any normal biological sample, wherein a subject exhibiting a significantly higher HRF polynucleotide expression level when compared with any normal biological sample is indicative of a subject having any endometriosis-related disease or as a subject at risk thereof. The specification and Oikawa teach studies of HRF gene expression in patients with endometriosis. Both studies demonstrate that HRF gene expression is not increased in endometrial tissue from endometriosis patients and they do not demonstrate a consistent or significant correlation between increased HRF gene expression in endometrial implants and endometrosis. Shalon teaches that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant.

Shalon further teaches that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels. Therefore, based on the data, it is unpredictable to associate HRF gene expression level with endometriosis. Further, Shalon teaches that a study of 20-50 different test individuals would be required to obtain statistically significant data and thus the skilled artisan would be required to perform a large study in order to determine of HRF gene expression level can be predictably/significantly correlated with endometriosis. This would require undue and unpredictable experimentation with no expectation of success.

Claims 1 and 6-8 are broadly drawn to methods of diagnosing any endometriosis-related disease by determining the expression level of histamine releasing factor (HRF) polynucleotide in an endometriotic tissue or menstrual blood biological sample and comparing the expression level with that in any normal biological sample, wherein a subject exhibiting a significantly higher HRF polynucleotide expression level when compared with any normal biological sample is indicative of a subject having any endometriosis-related disease or as a subject at risk thereof. The specification does not define what constitutes an expression level in a normal biological sample. Cheung teaches that there is natural variation in gene expression among different individuals and that a study of the expression of ACTG2 in 35 individuals varied by a factor of 17. Therefore, since gene expression levels can vary between

individuals, it is unpredictable to use any sample as a control to perform gene expression comparisons for diagnostic purposes. Further, the skilled artisan would be required to perform a large study in order to determine a normal expression level, such that a change in HRF expression level could be determined. This would require undue and unpredictable experimentation with no expectation of success.

Claims 1 and 6-8 are broadly drawn to methods of diagnosing any endometriosis-related disease by determining the expression level of histamine releasing factor (HRF) polynucleotide in an endometriotic tissue or menstrual blood biological sample and comparing the expression level with that in any normal biological sample, wherein a subject exhibiting a significantly higher HRF polynucleotide expression level when compared with any normal biological sample is indicative of a subject having any endometriosis-related disease or as a subject at risk thereof.

Claims 1 and 6-8 are broadly drawn to methods of diagnosing any endometriosis-related disease by determining the expression level of histamine releasing factor (HRF) polynucleotide in an endometriotic tissue or menstrual blood biological sample and comparing the expression level with that in any normal biological sample, wherein a subject exhibiting a significantly higher HRF polynucleotide expression level when compared with any normal biological sample is indicative of a subject having any endometriosis-related disease or as a subject at risk thereof. While the claims broadly read on correlating HRF gene expression with endometriosis-related disease in any organisms, the specification and Oikawa only teach studies in humans. Disease pathogenesis can vary between organisms and therefore, it is unpredictable

human data for associating gene expression with disease for diagnostic purposes in unstudied organisms.

Claims 1 and 6-8 are broadly drawn to methods of diagnosing any endometriosis-related disease by determining the expression level of histamine releasing factor (HRF) polynucleotide in an endometriotic tissue or menstrual blood biological sample and comparing the expression level with that in any normal biological sample, wherein a subject exhibiting a significantly higher HRF polynucleotide expression level when compared with any normal biological sample is indicative of a subject having any endometriosis-related disease or as a subject at risk thereof. The specification does not define endometriosis-related disease, and therefore the claims broadly read on diverse diseases such as cancer or infertility. The specification and Oikawa only teach studying HRF gene expression in patients with endometriosis. Therefore, the skilled artisan would be required to perform a large study in order to determine if HRF gene expression could be used diagnostically for other diseases. This would require undue and unpredictable experimentation with no expectation of success.

Conclusion

Given the lack of data from all organisms, the lack of significant HRF expression changes in the tissue studied, and the lack of normal expression value methods of diagnosing any endometriosis-related disease by determining the expression level of histamine releasing factor (HRF) polynucleotide in an endometriotic tissue or menstrual blood biological sample and comparing the expression level with that in any normal

biological sample, wherein a subject exhibiting a significantly higher HRF polynucleotide expression level when compared with any normal biological sample is indicative of a subject having any endometriosis-related disease or as a subject at risk thereof are replete with unpredictable experimentation that is considered undue.

Response to arguments

Applicants argue that sample from endometrial or menstrual tissue can be used diagnostically for the claimed method. This is not found persuasive, because, as described in the enablement rejection above, the disclosure does not contain any enabling subject matter.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jaime M. Greene whose telephone number is 571-270-3052. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jaime M. Greene

Jaime M. Greene 1/2/08

J. Goldberg

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